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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/050,376	01/16/2002	Uwe Joerg Rics	5/1312	6171

28505 7590 08/25/2003

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EXAMINER
ANDERSON, REBECCA L

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 08/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/050,376	RIES ET AL.	
	Examiner	Art Unit	
	Rebecca L Anderson	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *5 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-8* is/are rejected.

7)☒ Claim(s) *1-4 and 6-8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2 total* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-9 are currently pending in the instant application. Claims 1-4 and 6-8 are rejected and objected and claims 5 and 9 are withdrawn from consideration as being drawn to non-elected inventions.

Election/Restrictions

Applicant's election of Group I, claims 1-8 and the species of compound 4,

(4) N-(5-carbamimidoyl-2-hydroxy-benzyl)-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide,

in the paper mailed 02 July 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The election of compound 4, has resulted in the following generic concept: The product of the formula (I) wherein:

(i) m denotes the number 0,

n denotes the number 1,

A denotes an (unsubstituted) straight-chain C1-3 alkylene group,

R1 denotes a pyrrolidinocarbonyl

R2 denotes a hydrogen or an (unsubstituted) C1-3 alkyl group,

R3 denotes a hydrogen or a C1-3 alkyl group,

R4 denotes a hydrogen or an (unsubstituted) C1-3 alkyl group,

Ar denotes a phenyl group substituted by the groups R5, R6 and R7,

R5 denotes an (unsubstituted) amidino group,

R6 denotes hydroxy group and

R7 denotes a hydrogen or C1-3 alkyl group.

The remaining subject matter of claims 1-4, 6-8 that is not drawn to the elected invention identified supra and claims 5 and 9 stand withdrawn from consideration as being drawn to a non-elected invention, 37 CFR 1.142 (b).

The remaining compounds which are not within the generic concept, which are independent and distinct from the generic concept and do not have unity with the species elected and therefore are withdrawn by means of a restriction requirement within the claim are, for example, the compounds wherein:

(i) m denotes the number 0, n denotes the number 1, A denotes a straight chain C1-3 alkylene group wherein one or two hydrogen atoms independently of one another are replaced in each case by a C1-3 alkyl group or a hydrogen atom is replaced by the group –(CH2)p-Rf, or

(ii) m denotes the number 1,
n denotes the number 1 and

A denotes a bond or

(iii) m denotes the number 0 or 1,
n denotes the number 0 and
A denotes a straight-chain C_{1-3}-alkylene group wherein one or two hydrogen atoms independently of one another may be replaced in each case by a C_{1-3}-alkyl group, or

(iv) m denotes the number 2,
n denotes the number 0 and
A denotes a bond,

R_1 denotes an amino, C_{1-5}-alkylamino, C_{3-7}-cycloalkylamino or phenyl-C_{1-3}-alkylamino group each of which may be substituted at the amino nitrogen atom by a phenylcarbonyl or phenylsulphonyl group or by a C_{1-3}-alkyl or C_{1-3}-alkyl-carbonyl group optionally substituted in the alkyl moiety by a carboxy group, a group which may be converted *in vivo* into a carboxy group, an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a di-(C_{1-5}-alkyl)amino or N-(C_{3-7}-cycloalkyl)-C_{1-5}-alkylamino group, while the C_{1-5}-alkyl moiety with the exception of the 1 position may be substituted in each case by a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkyl-amino or di-(C_{1-3}-alkyl)-amino group,

an aminosulphonyl group optionally substituted by one or two C_{1-3}-alkyl groups,

a C_{3-7}-cycloalkyl-carbonyl group,

a phenylcarbonyl or heteroarylcarbonyl group,

or a C_{1-3}-alkyl group optionally monosubstituted by an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, hydroxy, phenyl or a 4- to 7-membered cycloalkyleneimino group or

terminally disubstituted by a phenyl group and a hydroxy group,

R2 denotes a fluorine, chlorine or bromine atom, a C1-3 alkyl group wherein the hydrogen atoms are wholly or partly replaced by fluorine atoms, a C2-3 alkenyl, C2-3 alkynyl, hydroxy, C1-3-alkoxy or trofluoromethoxy group,

R4 denotes a C1-3 alkyl group substituted by a carboxy group or a group which may be converted in vivo into a carboxy group and

Ar denotes a

Phenyl group substituted by the groups R5, R6 and R7

wherein R5 denotes a cyano group an amidino group substituted by one or two C1-3 –alkyl groups, an amino-C1-3-alkyl, C1-3 alkylamino-C1-3-alkyl or di-(C1-3-alkyl)amino-C1-3-alkyl group,

R_6 denotes a hydrogen, fluorine, chlorine or bromine atom, a trifluoromethyl, C1-3 alkyl, hydroxy-C_{1-3}-alkyl, C_{1-3}-alkoxy, C_{1-3}-alkoxy-C_{1-3}-alkyl, carboxy, carboxy-C_{1-3}-alkyl, carboxy-C_{1-3}-alkoxy, C_{1-4}-alkoxy-carbonyloxy, C_{1-4}-alkoxy-carbonyl-C_{1-3}-alkoxy, phenyl-C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)amino group and

R7 denotes a fluorine, chlorine or bromine atom,

Naphthyl group substituted by the groups R5, R6 and R7,

or a thienyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl group optionally substituted in the carbon skeleton by a C_{1-3}-alkyl group,

or a 6-membered heteroaryl group which contains one or two nitrogen atoms,

Some specific species of the withdrawn compounds are the species of example

(11) N-(5-carbamimidoyl-2-hydroxy-benzyl)-3-methyl-4-[N-cyclopentyl-N-(3-ethoxy-carbonyl-propionyl)amino]-benzamide,

(12) N-(5-carbamimidoyl-2-hydroxy-benzyl)-3-methyl-4-(N-acetyl-N-cyclobutylamino)-benzamide,

(13) N-(5-carbamimidoyl-2-hydroxy-benzyl)-3-methyl-4-(N-cyclopentyl-N-methyl-amino)-benzamide,

(14) N-(5-carbamimidoyl-2-hydroxy-benzyl)-3-methyl-4-[N-cyclopentyl-N-(3-carboxy-propionyl)amino]-benzamide,

(15) N-(5-carbamimidoyl-2-hydroxy-benzyl)-4-cyclopentylamino-3-methyl-benzamide,

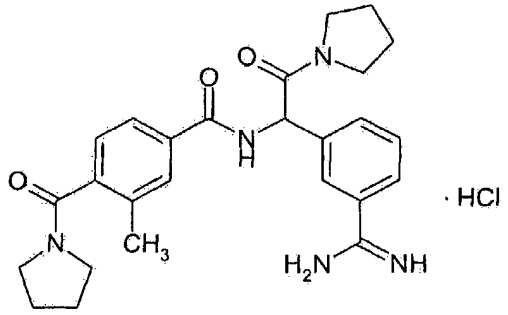
(18) N-(5-carbamimidoyl-2-hydroxy-benzyl)-3-methyl-4-[N-(2-aminoacetyl)-N-cyclopentyl-amino]-benzamide,

(19) N-(5-carbamimidoyl-2-hydroxy-benzyl)-3-methyl-4-[N-(3-amino-propionyl)-N-cyclopentyl-amino]-benzamide,

(23) ethyl 3-(3-carbamimidoyl-phenyl)-3-{3-methyl-4-[N-(3-amino-propionyl)-N-cyclo-pentyl-amino]-benzoylamino}-propionate,

and

(1) N-[1-(3-carbamimidoyl-phenyl)-2-oxo-2-(pyrrolidin-1-yl)-ethyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide-hydrochloride



· HCl

, etc.

The above mentioned withdrawn compounds which are withdrawn from consideration as being for non elected subject matter differ materially in structure and composition from the compounds of the elected invention. The withdrawn compounds contain varying functional groups which differ from those of the elected invention such as thienyl, thiazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, etc. which are chemically recognized to differ in structure and function. This recognized chemical diversity of the functional groups can be seen by the various classification of these functional groups in the U.S. classification system, i.e. class 549 subclass 29(+) (thienyl), class 548 subclass 146(+) (thiazolyl), class 544 subclass 242(+) (pyrimidinyl), class 544 subclass 336(+) (pyrazinyl), class 544 subclass (224(+) (pyridazinyl), etc. Therefore, again, the compounds which are withdrawn from consideration as being for non elected subject matter differ materially in structure and composition and have been restricted properly

as a reference which anticipated but the elected subject matter would not even render obvious the non-elected subject matter.

These withdrawn compounds are independent and distinct from the elected invention and do not have unity with the species elected and are therefore withdrawn by means of a restriction requirement within the claims.

Applicants' claims involve more than one independent or distinct invention. Under 35 U.S.C. 121, the claims may be restricted and the examination limited to a restricted invention.

The withdrawn subject matter of claims 1-9 is properly restricted as it differs materially in structure and element from the elected subject matter identified supra so as to be patentably distinct there from. A reference, which anticipated but the elected subject matter would not even render obvious the non-elected subject matter. Accordingly, restriction, as has been required is proper.

Claim Objections

Claims 1-4, 6-8 are objected to as containing non-elected subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 and 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/71512.

Applicants instant elected invention in claims 1-4 and 6-8 teach the compound of the formula (I) wherein

(i) m denotes the number 0,

n denotes the number 1,

A denotes an (unsubstituted) straight-chain C1-3 alkylene group,

R1 denotes a pyrrolidinocarbonyl

R2 denotes a hydrogen or an (unsubstituted) C1-3 alkyl group,

R3 denotes a hydrogen or a C1-3 alkyl group,

R4 denotes a hydrogen or an (unsubstituted) C1-3 alkyl group,

Ar denotes a phenyl group substituted by the groups R5, R6 and R7,

R5 denotes an (unsubstituted) amidino group,

R6 denotes hydroxy group and

R7 denotes a hydrogen or C1-3 alkyl group. (claims 1, 2),

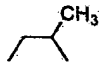
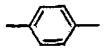
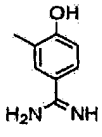
wherein R1 is bound in the 4 position to the phenyl group contained in the formula, A denotes a methylene group and R5 is bound in the 3 position if R6 denotes a hydrogen on the phenyl group for Ar (claim 3), wherein R1 is bound in the 4th position of the phenyl group, R2 is bound in the 3 position if R 3 is a C1-3-alkyl group in the 5 position (claim 4) and the specific compounds as found in claim 6, for example

(4) N-(5-carbamimidoyl-2-hydroxy-benzyl)-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide,

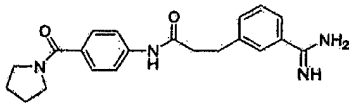
Claim 7 teaches physiologically acceptable salt of the compound of formula (I) and claim 8 teaches a pharmaceutical composition of the compound of formula (I).

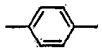
Determining the scope and contents of the prior art

The prior art WO 00/71512 discloses compounds of the formula A-Y-D-E-G-J-Z-L (pages 4) which are useful for the treatment of disease states (page 10) characterized by undesired thrombosis. Page 16 of the prior art discloses a preferred embodiment for the compound of formula A-Y-D-E-G-J-Z-L wherein G is selected from –CR7R8 and –CR7aR8a-CbR8b (page 18). A further preferred embodiment found on page 26

discloses the compound of formula A-Y-D-E-G-J-Z-L wherein G can be  (page 29). A further preferred embodiment of the compound of formula A-Y-D-E-G-J-Z-L is found on page 31 wherein A can be  , Y can be –C(=O)-, D can be  , E can be –C(=O)-N(-H)-, J is a direct link (page 32), and Z-L can be  . Page 94 of the prior art reference discloses the compound of example 24:

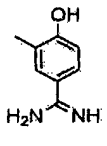
Example 24. Preparation of N-[4-(1-pyrrolidinylcarbonyl)phenyl]-3-(3-amidinophenyl)-propionamide.



which has a value for A corresponding to  , a value for Y corresponding to –C(=O)-, a value for D corresponding to  , a value for G corresponding to –Ch2-CH2-, a value for J corresponding to a direct link. This species example disclose further preferences towards these specific values. Pages14 and 15of the prior art discloses pharmaceutically acceptable salts of the compounds of the formula A-Y-D-E-G-J-Z-L such as acid addition salts and base addition salts. Pages 53 and 54 disclose pharmaceutical compositions comprising the compound of the formula A-Y-D-E-G-J-Z-L

and provides specific acceptable carriers, excipients and stabilizers and a preferred dosage.

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art and the instant elected invention is that the prior art does not disclose a specific species example which falls within applicants instant elected invention. The prior arts example 24 differs from the instantly elected invention in the value for E and the value for Z-L, but there are other preferred embodiments of the prior art invention which have the value for E as –C(=O)-N(-H)-, and the value for Z-L as  as discussed above. Also, the prior art does generically disclose the compound of A-Y-D-E-G-J-Z-L which encompasses applicants instant invention and provides ample direction and guidance in the form of preferred embodiments as to the preferred substituents for A, Y, D, E, G, J, Z and L.

Resolving the level of ordinary skill in the pertinent art and considering objective evidence present in the application indicating obviousness or nonobviousness

Minus a showing of unobvious results, it would have been obvious to one of ordinary skill in the art at the time of the invention to create compounds which fall within applicants elected invention in order to prepare more compounds as found in the prior art of WO 00/71512 for antithrombotic treatment. The motivation is found in the prior art of WO 00/71512 which provides ample direction and guidance in the form of preferred embodiments and specific examples, and therefore, provides the motivation to prepare the compounds of applicants instant elected invention since these are the preferred

compounds of WO 00/71512. The motivation is to prepare more compounds which are useful for antithrombotic treatment.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (703) 605-1157. Mrs. Anderson can normally be reached Monday through Friday 7:00AM to 3:30PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph McKane, can be reached at (703) 308-4537.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone numbers are (703) 308-1235 and (703) 308-0196.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45AM to 4:45PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4242, (703) 305-3592, and (703) 305-3014.

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